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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of: Steven R. Wiley

Docket No.: 2968-B

Group Art Unit: 1642

Serial No: 09/742,454

Examiner: Yaen, C.H.

Filed: December 19, 2000

For: TWEAK RECEPTOR

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, the undersigned, hereby declare that:

1. I am familiar with the above-captioned patent application, being the inventor of the invention disclosed and claimed therein.

2. I have studied the tumor necrosis factor ("TNF") family of ligands and receptors since 1995. A copy of my *curriculum vita* and a selected list of my publications are provided in Exhibit A.

3. In the above-captioned application and its siblings, I revealed for the first time that the TWEAK receptor is a member of the tumor necrosis factor receptor super family ("TNFRSF") and that its extracellular domain contains one copy of a cysteine-rich repeat, a motif that is common to the TNFRSF.

4. As of December, 1999, it was well known that the function of the extracellular domains of the TNFRSF is binding ligand.

5. As of December, 1999, the structure of the TNFRSF extracellular domain also was well known. The extracellular domains of many TNFRSF members have only a low level of overall amino acid sequence similarity to each other. However, the family is characterized by the presence of one to six copies of an approximately 40 amino acid residue cysteine-rich repeat motif in the extracellular ligand binding domain. The consensus sequence for these cysteine-rich repeats is Cys1-x_{10-15}-Cys2-x_2-Cys3-x_2-Cys4-x_{8-11}-Cys5-x_{7-8}-Cys6, although more distantly related members of the superfamily deviate

somewhat from this formula. These cysteine residues form a network of disulfide bonds that gives the TNFSF ligand binding domains a characteristic tertiary structure, in spite of their diverse primary sequences.

6. The TWEAK receptor cysteine-rich repeat has the sequence Cys1-x_{12}-Cys2-x_2-Cys3-x_2-Cys4-x_8-Cys5-x_2-Cys6, which is very close to the TNFRSF consensus sequence.

7. The structure-function relationship of the TNFRSF extracellular domains also was well known as of December, 1999. Specifically, at least three lines of evidence showed that TNFRSF members bind ligand via their cysteine-rich repeats.

8. First, X-ray crystallographic analysis of the extracellular domain of TNF receptor bound to ligand showed that the ligand was bound to cysteine-rich repeats of the extracellular domain.

9. Second, soluble, ligand-binding fragments of TNFRSF members were known in the art. As early as 1996, the list of TNFRSF members known to have naturally-occurring ligand-binding soluble forms included TNFR1, TNFR2, Fas, CD27, CD30, CD40, 4-1BB, and NGFR. Other soluble TNFRSF homologs were known to be expressed by viruses and to suppress the host immune response by binding and sequestering TNF. Furthermore, as of December, 1999, recombinant soluble TNFRSF members that contained the cysteine-rich repeats had been made and shown to bind to ligand.

10. One recombinant TNFRSF molecule, etanercept (ENBREL®, Amgen, Inc., Thousand Oaks, CA), a soluble TNF receptor comprising cysteine-rich repeats, was so well characterized that in 1998 the United States Food and Drug Administration approved it for therapeutic use in humans. According to the ENBREL® website (www.enbrel.com/index.jsp), since its approval, ENBREL® has been used by over 200,000 people.

11. Third, deletion analysis of osteoprotegrin ("OPG"; also known as osteoclastogenesis inhibitory factor), a naturally occurring soluble TNFRSF member, showed that mutated OPG with intact cysteine-rich repeats bound to ligand, but that mutated OPG with disturbed repeats did not.

12. Thus, as of December, 1999, it was known in the art that for TNFRSF members the function of binding ligand is mediated by the structure of cysteine-rich repeats.

13. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

4/15/04
Date

Steven R. Wiley

Exhibit A

Curriculum Vita for Dr. Steven R. Wiley, Ph.D.

Education:

Ph.D., Molecular and Cellular Biology program, University of Wisconsin, 1993.
B.S., major Mathematics, University of Chicago, 1986.

Employment:

Research Scientist IV, Amgen Corp 2002-2004
Senior Staff Scientist, Immunex Corp, 1998-2002
Associate Staff Scientist, Abbott Laboratories, 1996-1998
Postdoctoral Fellow, Immunex Corp, 1993-1996
Software Developer, Enabling Technologies Corp, 1986-1988

Overview:

I have years of experience studying, publishing and speaking about experimental protein therapeutics with a wide range of activities and uses, specifically those related to the TNF ligand and receptor.

Selected Patents and Published Applications:

WO02079474	Human B7 Polypeptides
WO02072769	Human Serpin Polypetpides
AU2318202	Hematopoietin Receptors hpr1 and hpr2
AU8497701	Claudin Polypeptides
AU8084301	A human Disintegrin Protein
AU7906001	Metalloproteinase-Disintegrin Polypeptides And Methods Of Making And Use Thereof
AU2731501	Tweak Receptor
US6207642	Member Of The TNF Family Useful For Treatment And Diagnosis Of Disease
EP0994966	Member Of The TNF Family Useful For Treatment And Diagnosis Of Disease
WO9835061	Member Of The TNF Family Useful For Treatment And Diagnosis Of Disease
NZ311982	TNF Related Apoptosis Inducing Ligand (TRAIL), A Method For Producing Them And Associated Antibodies

Selected Publications:

Wiley SR, Cassiano L, Lofton T, Davis-Smith T, Winkles JA, Lindner V, Liu H, Daniel TO, Smith CA, Fanslow WC
A novel TNF receptor family member binds TWEAK and is implicated in angiogenesis
Immunity. 2001 Nov;15(5):837-46

Sedger LM, Shows DM, Blanton RA, Peschon JJ, Goodwin RG, Cosman D, Wiley SR.
IFN-gamma mediates a novel antiviral activity through dynamic modulation of TRAIL and TRAIL receptor expression
J Immunol. 1999 Jul 15;163(2):920-6

Griffith TS, Wiley SR, Kubin MZ, Sedger LM, Maliszewski CR, Fanger NA.
Monocyte-mediated tumoricidal activity via the tumor necrosis factor-related cytokine, TRAIL
J Exp Med. 1999 Apr 19;189(8):1343-54

Lynch CN, Wang YC, Lund JK, Chen YW, Leal JA, Wiley SR.
TWEAK induces angiogenesis and proliferation of endothelial cells
J Biol Chem. 1999 Mar 26;274(13):8455-59

Wiley SR
Genomics in the real world (Review)
Curr Pharm Des. 1998 Oct;4(5):417-22

Wiley SR, Goodwin RG, Smith CA.
Reverse signaling via CD30 ligand
J Immunol. 1996 Oct 15;157(8):3635-39

Wiley SR, Schooley K, Smolak PJ, Din WS, Huang CP, Nicholl JK, Sutherland GR, Smith TD, Rauch C, Smith
Identification and characterization of a new member of the TNF family that induces apoptosis
Immunity. 1995 Dec;3(6):673-82

APPENDIX

Cited References:

Bazzoni *et al.*, 1996, New England J Med. 334:1717-25

Garrison *et al.*, 1999, Ann Rheum Dis 58 (Suppl I):I65-I69

Lotz *et al.*, 1996, J Leukoc Biol. 60:1-7

Naismith *et al.*, 1996, J Inflamm. 47:1-7

Naismith *et al.*, 1998, TIBS 23:74-79

van Ostade *et al.*, 1994, Protein Eng. 7:5-22

Simonet *et al.*, 1997, Cell 89:309-19

Wallach *et al.*, 1991, Agents Actions Suppl. 35:51-57

Yamaguchi *et al.*, 1998, J Biol Chem 273:5117-23